

# SENSITIVITY OF GONOCOCCI TO ANTIBIOTICS RELATED TO RESULTS OF TREATMENT\*

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In recent years a decreasing sensitivity of gonococci to antibiotics, especially to penicillin, has been reported. It has been observed in Denmark by Reyn, (1961) and Nielsen and Schmidt (1962). It has also been demonstrated that phagocytosed gonococci are resistant to far higher concentrations of penicillin than non-phagocytosed gonococci (Thayer, Perry, Field, and Garson, 1957).

## Material

This series includes 980 patients, representing 1,103 infections, who were treated at the Rudolph Bergh Hospital for gonorrhoea during the 3-year period 1961 to 1963; They constitute 8.7 per cent. of all cases notified in the municipality of Copenhagen in that period.

The distribution of the patients by sex is given in Table I, which also shows the numbers treated as in-patients.

TABLE I  
NUMBER OF PATIENTS AND INFECTIONS, BY SEX

Sex .. .. .	Female		Male	
	No.	Per cent.	No.	Per cent.
Patients .. .. .	373	38.1	607	61.9
Infections .. .. .	427	38.7	676	61.3
Treated as In-patients ..	127	11.5	26	2.4

Of this series, 878 were domiciled in Copenhagen and 26 in other parts of Denmark, while 49 were foreigners, including thirteen seamen. In all, 115 foreign and Danish seamen were treated. 136 were women referred by the police under the Danish Venereal Diseases Act, and most of these were admitted as in-patients.

In a total of 594 cases sensitivity determinations were carried out before the first treatment; in 1961 this was not a routine procedure and was done in only 97 cases, but by 1963 it had become routine and was done in 263 cases (81.2 per cent). These determinations were performed in the State Serum Institute, Copenhagen against penicillin, streptomycin, and tetracycline. (Table II, and

TABLE II  
PERCENTAGE SENSITIVITY OF GONOCOCCI IN PER CENT. OF THE STRAINS STUDIED, 1961 AND 1963

Drug	Dosage (μg.)	Sensitivity	1961 (97 cases)	1963 (263 cases)
Penicillin	0.038	Sensitive	49.5	54.5
Streptomycin	25	Sensitive	67	81.3
Tetracycline	1.05	Sensitive	74.2	89.4
Penicillin	0.038	Reduced sensitivity	50.5	45.6
Streptomycin	25	Resistant	33	18.6
Tetracycline	1.05	Reduced sensitivity	25.8	10.6

Figs 1, 2, and 3 (overleaf)); the values indicate the concentration required for a 50 per cent. inhibition assessed by the plate dilution method. The graphs were worked out by the Kärber method.

The follow-up period was 4 weeks, *i.e.* if gonococci were found more than 4 weeks after the last positive finding, the case was recorded as a new case. Cultures were made as a routine from the urethra in males, from the urethra and cervix in women, and from the rectum in only a small number of cases. In most cases, two negative cultures had been obtained in the males and three in the females before they were discharged.

## Methods of Treatment

**Penicillin.**—In 659 cases 0.3 m.u. procaine penicillin was administered as the first treatment. "Standard mega doses" of penicillin, (*i.e.* procaine penicillin 1.2 m.u. plus crystalline penicillin G, 1 m.u., daily for 3 days) were given as the *first* treatment in ninety cases, 22 of which had been treated ineffectively with penicillin before they were seen by us. Sensitivity tests before treatment had revealed a reduced sensitivity to penicillin in 46 cases, and five patients had complications.

"Standard mega doses" of penicillin were given as the *second* treatment in 84 cases, 72 of which had received 0.3 m.u. procaine penicillin with no effect. In four instances, "standard mega doses" of penicillin were given as the *third* treatment. For these "standard mega doses", we have since November, 1963, been using a

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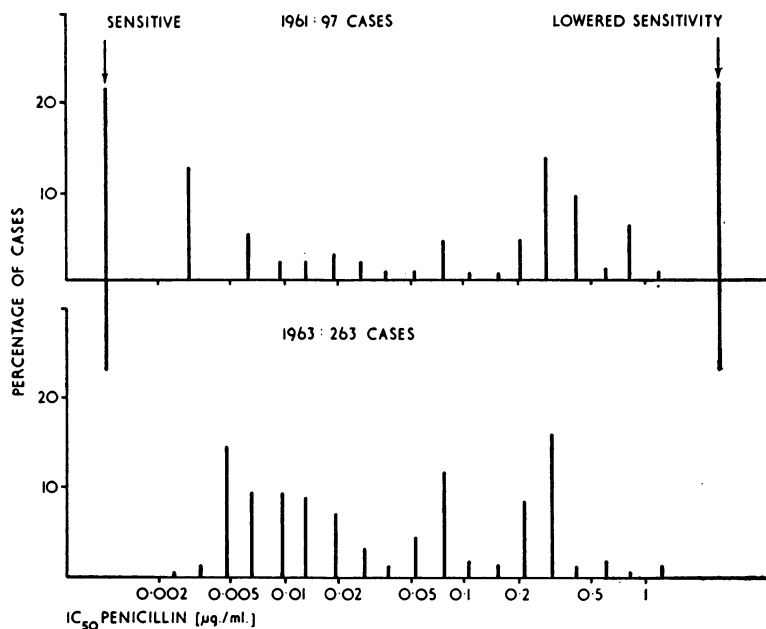


FIG. 1.—Sensitivity to penicillin at first treatment in 97 cases from 1961 and 263 cases from 1963.

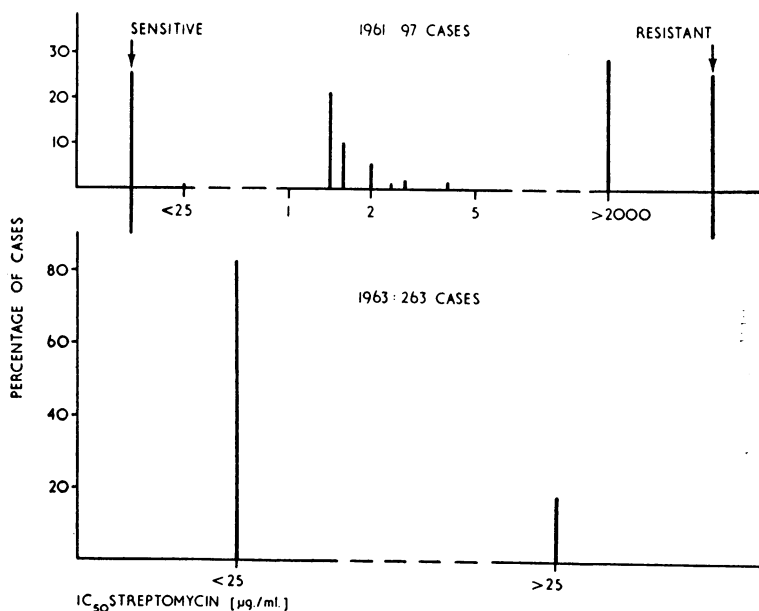


FIG. 2.—Sensitivity to streptomycin at first treatment in 97 cases from 1961 and 263 from 1963.

preparation from Leo Pharmaceutical Products Ltd., Copenhagen, containing procaine penicillin and penicillin G as described above in powder form, soluble in 3 ml. water. Twelve patients received 3 m.u. procaine penicillin, as a single injection.

*Streptomycin.*—1 g. daily for 3 days was administered as the first treatment in 105 cases, 42 of which were in women referred by the police. Such patients are now treated routinely with streptomycin in order to avoid masking a possible co-existing syphilis. In 22 of the other

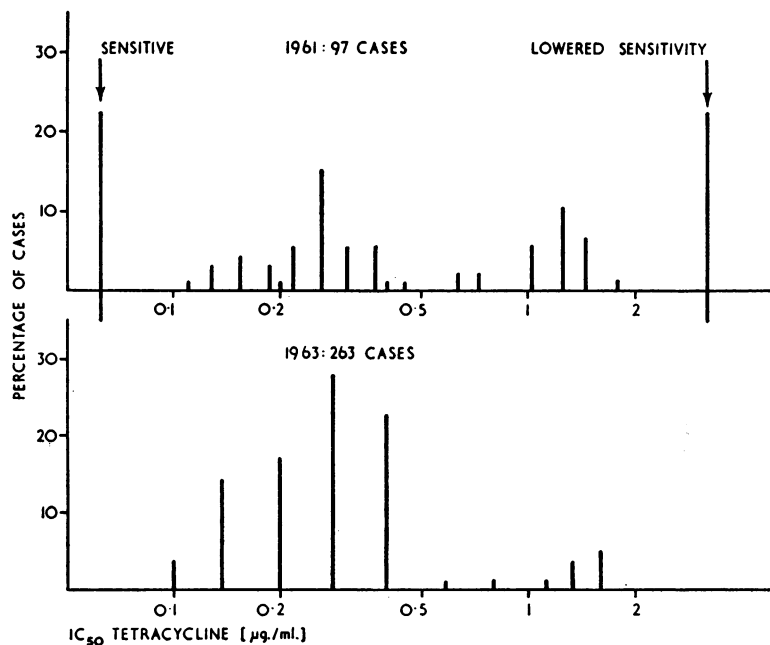


FIG. 3.—Sensitivity to tetracycline at first treatment in 97 cases from 1961 and 263 cases from 1963.

63 patients who received streptomycin there was a suspicion of syphilis, thirteen were allergic to penicillin, and 51 had shown a reduced sensitivity to penicillin. For one or more of these reasons streptomycin was preferred as the first treatment.

**Tetracycline.**—250 mg. four times daily for 4 days, was administered as the first treatment to 23 patients, seven of whom were allergic to penicillin, while ten had received penicillin elsewhere without effect before being referred to us.

### Results

#### Penicillin

**Procaine Penicillin, 0.3 m.u.**—The results in the 659 cases are shown in Table III. In eighteen of the 135 cases not cured, the history gave rise to a

suspicion of re-infection. Of the 448 cured cases, 198 had had sensitivity determinations before treatment (Table IV, overleaf); 55 (27.8 per cent.) of these cases were cured, although they were infected with gonococci having a reduced sensitivity ( $IC_{50} > 0.38 \mu g/ml$ ). Three of the last-mentioned patients made only one follow-up visit; the remainder came twice or three times.

Of the 135 uncured cases, 72 had had sensitivity determinations before treatment (Table IV); sixteen were sensitive, while 56 showed a reduced sensitivity to penicillin. Of the sixteen sensitive cases, seven showed unchanged sensitivity when re-treated, while in three the sensitivity had altered. In two cases there was probably a question of a "ping-pong"

TABLE III  
RESULTS OF TREATMENT WITH VARIOUS DRUGS AT STATED DOSAGES

Drug	Dosage	Cases Treated	Result		
			Cured	Not Cured	Not Followed
Procaine Penicillin . . . .	0.3 m.u.	No. 659 Per cent.	448 68.0	135 20.5	76 11.5
Penicillin as First Treatment	"Standard mega doses"	No. 90 Per cent.	81 90.0	1 1.1	8 8.9
Penicillin as Second Treatment	"Standard mega doses"	No. 84 Per cent.	74 88.1	2 2.4	8 9.5
Streptomycin . . . . .	1 g. daily for 3 days	No. 105 Per cent.	79 75.2	20 19.1	6 5.7
Tetracycline . . . . .	250 mg. four times a day for 4 days	No. 23 Per cent.	18 78.3	3 13.0	2 8.7

TABLE IV

SENSITIVITY TO PENICILLIN IN 270 PATIENTS WHO RECEIVED 0.3 m.u. PROCAINE PENICILLIN AS THE FIRST TREATMENT

IC 50 Penicillin ( $\mu\text{g./ml.}$ )	Cured	Not Cured
Sensitive (not further specified)	11	4
0.0024	1	0
0.0033	3	0
0.0047	44	2
0.0066	22	4
0.0094	15	0
0.0106	0	1
0.0132	21	2
0.0188	15	1
0.027	6	0
0.037	5	2
0.053	2	2
0.075	23	7
0.106	4	2
0.15	2	1
0.21	10	12
0.30	12	20
0.42	0	7
0.60	1	2
0.84	1	1
1.20	0	1
Reduced Sensitivity (not further specified)	0	1
Total .. .. .	198	72

re-infection, and in another two the history indicated re-infection. Thus, re-infection was probable, or possible, in at least seven cases, and three of

these were later cured by penicillin in the same dosage. No complications were found in these sixteen cases.

Fig. 4 records the cure rate, in relation to the sensitivity of the gonococcal strains, when 0.3 m.u. procaine penicillin was used as the *first* treatment.

*Penicillin in "Standard Mega Doses".*—The results in the ninety cases receiving this as the *first* treatment are shown in Table III. The one case not cured had three negative cultures after this first treatment, and when gonococci were again found the sensitivity had altered, so that this case must be considered as cured and re-infected. Thus, the cures amount to 82 (91 per cent.) in this group. The 62 available sensitivity determinations are shown in Table V (opposite).

*Penicillin in "Standard Mega Doses".*—The results in the 84 cases receiving this as the *second* treatment are shown in Table III. In one of the two cases not cured there was presumably a "ping-pong" re-infection; the other had had a "new suspicious intercourse" after treatment, and the sensitivity differed at the first and third treatment (no determination was made at the second treatment). The

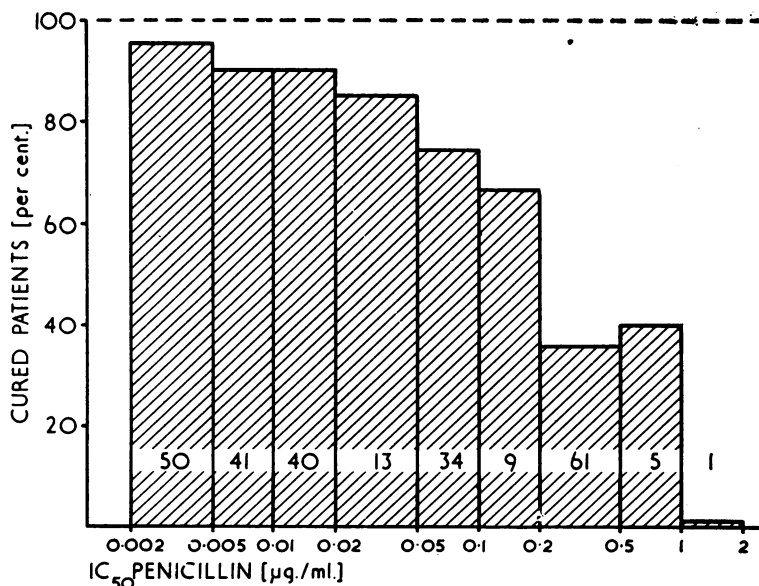


FIG. 4.—Cure rate when 0.3 m.u. procaine penicillin was the first treatment. The figures above the abscissa indicate the number of patients represented by each individual column.

TABLE V  
SENSITIVITY TO PENICILLIN IN 62 PATIENTS WHO  
RECEIVED PENICILLIN IN "STANDARD MEGA DOSES"  
AS THE FIRST TREATMENT

IC 50 Penicillin ( $\mu\text{g./ml.}$ )	Cured	Not Cured
0.0047	10	
0.0066	2	
0.0094	4	
0.0132	2	
0.0188	2	
0.027	1	
0.053	4	
0.075	6	
0.106	3	
0.15	1	
0.21	3	
0.30	15	
0.42	6	
0.60	1	
1.2	1	
Total .. .. .	61	1

62 available sensitivity determinations are given in Table VI.

TABLE VI  
SENSITIVITY TO PENICILLIN IN 62 PATIENTS WHO  
RECEIVED PENICILLIN IN "STANDARD MEGA DOSES"  
AS THE SECOND TREATMENT

IC 50 Penicillin ( $\mu\text{g./ml.}$ )	Cured	Not Cured
0.0066	1	
0.0094	2	
0.0132	1	
0.027	1	
0.038	2	
0.053	1	
0.075	10	
0.106	4	
0.15	3	
0.21	6	
0.30	21	
0.42	4	
0.60	3	
0.84	2	
Total .. .. .	61	1

*Penicillin in "Standard Mega Doses".*—Four patients received this as the **third** treatment, and three were cured. The one patient who was not cured was infected with gonococci having an IC 50 for penicillin of 0.42  $\mu\text{g./ml.}$  Culture was negative once after the treatment, and the patient was almost symptom-free for 25 days, after which gonococci were again found to be present. The same treatment was then repeated, and he showed negative cultures on two occasions and was presumed to be cured.

*Procaine Penicillin, 3 m.u.*—Twelve patients received this as a single injection, as suggested by (Knudsen and Perdrup, 1963); nine were cured, two did not attend follow-up, and one was not cured. This last patient had prostatitis and was subsequently cured with 500 mg. tetracycline, three times daily for 5 days + fever vaccine.

*Streptomycin.*—The results in the 105 cases given streptomycin 1 g. daily for three days as the *first* treatment are shown in Table III. In 93 of them sensitivity determinations were carried out before the first treatment and Table VII gives the results for the 87 who were followed. Two with sensitive strains who were not cured both had a positive gonococcal complement-fixation test, but no clinical complications. One patient with resistant gonococci was cured, four negative cultures being obtained before discharge.

TABLE VII  
SENSITIVITY TO STREPTOMYCIN IN RELATION TO  
THERAPEUTIC RESULTS IN 87 PATIENTS

IC 50 Streptomycin ( $\mu\text{g./ml.}$ )	Cured	Not Cured
25 (sensitive)	46	2
1.41	15	
1.68	1	
2.0	3	
2.4	1	
2.8	1	
25 (resistant)	1	10
2000 (resistant)		7
Total .. .. .	68	19

*Tetracycline.*—The results in the 23 who received tetracycline, 250 mg. four times daily for 4 days are shown in Table III. Nineteen had sensitivity determinations before treatment, but two of these failed to attend follow-up (Table VIII). Two patients with IC 50 1.49  $\mu\text{g./ml.}$  were not cured; both were males, and one was an in-patient. The gonococcal complement-fixation test was positive in both cases, but there were no clinical complications. The one patient with IC 50 0.28  $\mu\text{g./ml.}$  who was not cured was an

TABLE VIII  
SENSITIVITY TO TETRACYCLINE IN RELATION TO  
THERAPEUTIC RESULTS IN 17 PATIENTS

IC 50 Tetracycline ( $\mu\text{g./ml.}$ )	Cured	Not Cured
Sensitive (not further specified)	1	
0.14	1	
0.186	1	
0.20	1	
0.26	1	
0.28	1	
0.31	1	
0.40	3	
0.53	2	
1.33	1	
1.49	1	2
Total .. .. .	14	3

out-patient, and admitted that he had had intercourse between treatment and follow-up.

### Conclusion

In the present series, 0.3 m.u. procaine penicillin given as the first treatment cured 76.8 per cent. of the patients followed.

These results are in keeping with the sensitivity findings, but it is surprising to note that 55 patients cured by this dosage showed reduced sensitivity.

With penicillin in "standard mega doses", given as the first or second treatment the cure rate was close on 100 per cent. of the patients followed—although this group included 77·4 per cent. in which the gonococci showed reduced sensitivity.

In 105 cases treated with streptomycin, cure was obtained in 79·8 per cent. of those who attended follow-up and the conformity with the sensitivity tests was so close that it seems useless to give streptomycin if the sensitivity determination shows resistance. Conversely, the probability of cure with streptomycin in this dosage is very high if the gonococcal strain is sensitive. This means that the prognosis can be foretold as soon as the report on the sensitivity test is received—about 5 days after treatment has been instituted.

As far as tetracycline is concerned, it is not possible to make far-reaching deductions from this small series, but it was successful in two out of four cases with reduced sensitivity (*i.e.* IC 50 > 1·05 µg./ml.).

### Discussion

In the treatment of gonorrhoea the desirability of efficacy must always be weighed against the risk of masking syphilis which may have been acquired at the same time. To this problem streptomycin offers the best solution, but with this treatment the patients have to attend for 3 consecutive days.

As has been demonstrated above, almost the same cure rate may be obtained by 0·3 m.u. procaine penicillin; it must be borne in mind that more of the patients treated with streptomycin were in-patients, so that re-infections were presumably fewer.

This type of penicillin therapy has the advantage of requiring only one injection, but even this small dose will mask co-existing syphilis, and the "standard mega doses" are even more liable to mask syphilis although a cure rate of almost 100 per cent. of the gonorrhoea is obtained. This leads us to the question how far the follow-up can—and should—be carried. When the "standard mega doses" are given a few days after the initial infection, a simultaneous cure of gonorrhoea and syphilis is likely, but in cases coming for re-treatment of gonorrhoea, syphilis may have been acquired several weeks previously, and may have reached the secondary stage when masking has become a serious problem.

### Summary

1,103 patients with gonorrhoea were treated at the Rudolph Bergh Hospital, Copenhagen, during the

period 1961 to 1963. Of 659 who received 0·3 m.u. procaine penicillin as the first treatment, 76·8 per cent. of those followed were cured.

Among the 174 patients who received procaine penicillin 1·2 m.u. plus sodium penicillin 1·0 m.u. daily for 3 days as the first treatment or first re-treatment, the cure rate was close on 100 per cent.

On the whole, there was conformity between determinations of the sensitivity of the gonococci and the results obtained by 0·3 m.u. procaine penicillin.

Out of 105 patients who received streptomycin 1 g. daily for 3 days as the first treatment, 79·8 per cent. of those followed were cured. In this group there was about 95 per cent. conformity between the therapeutic results and the sensitivity determinations.

Out of 23 patients who were treated with tetracycline 250 mg. four times daily for 4 days as the first treatment, 85·7 per cent. of those followed were cured.

### REFERENCES

- King, A. (1960). *Brit. J. vener. Dis.*, **36**, 34.  
 — and Nicol, C. (1964). "Venereal Diseases". Cassell, London.  
 Knudsen, H. Ekkert, and Perdrup, A. (1963). *Acta dermat. venerol. (Stockh.)*, **43**, 235.  
 Lanigan-O'Keefe, F. M. (1963). *Brit. J. vener. Dis.*, **39**, 241.  
 Nielsen, K., and Schmidt, H. (1962). *Månedsskr. prakt. Lægegern.*, **40**, 336.  
 Reyn, A. (1961). *Brit. J. vener. Dis.*, **37**, 145.  
 Schmidt, H. (1961). *Ugeskr. Læg.*, **123**, 749.  
 Thayer, J. D., Perry, M. I., Field, F. W., and Garson, W. (1957). "Antibiotics Annual, 1956-1957", p. 513. Medical Encyclopaedia, New York.

### Étude de la sensibilité des gonocoques aux antibiotiques par rapport aux résultats thérapeutiques.

#### RÉSUMÉ

1,103 patients atteints de gonorrhée furent traités à l'hôpital Rudolph Bergh de Copenhague pendant la période 1961-1963. Des 659 qui reçurent 0,3 m.u. de pénicilline procaine comme premier traitement, 76,8% furent guéris.

Parmi les 174 patients qui reçurent 1,2 m.u. de pénicilline procaine, plus 1,0 m.u. de sodique pénicilline pendant 3 jours comme premier traitement, le taux de succès fut de presque 100%.

Dans l'ensemble il y eut une correspondance entre la sensibilité du gonocoque aux antibiotiques et les résultats obtenus en donnant 0,3 m.u. de pénicilline procaine.

Parmi les 105 patients qui reçurent 1 g. de streptomycine par jour pendant 3 jours comme premier traitement, 79,8% furent guéris. Dans ce groupe la corrélation entre les résultats thérapeutiques et la sensibilité aux antibiotiques fut aux environs de 95%.

Parmi les 23 patients qui furent traités par 250 mg. de tétracycline 4 fois par jours pendant 4 jours, comme premier traitement, 85,7% furent guéris.